

What is claimed is:

1. A method of analyzing a first nucleic acid sample comprising:
providing said first nucleic acid sample;
reproducibly reducing the complexity of said first nucleic acid sample to produce a
second nucleic acid sample which may comprise a plurality of non-identical sequences
whereby said second nucleic acid sample is obtainable by:

fragmenting said first nucleic acid sample to produce fragments and ligating
adaptor sequences to said fragments;

fragmenting said first nucleic acid sample to produce fragments, denaturing
said fragments, allowing some of said fragments to reanneal to form double stranded
DNA sequences and removing said double stranded DNA sequences.

amplification by arbitrarily primed PCR;
hybridizing said first nucleic acid sample to an oligonucleotide probe bound
to a solid support;

hybridizing said first nucleic acid sequence to a mismatch binding protein;
providing a nucleic acid array;

hybridizing said second nucleic acid sample to said array; and
analyzing a hybridization pattern resulting from said hybridization.

20 2. The method of claim 1 wherein said second nucleic acid sample comprises at least
0.5 % of said nucleic acid sample

3. The method of claim 1 wherein said second nucleic acid sample comprises at
least 3 % of said nucleic acid sample

25 4. The method of claim 1 wherein said second nucleic acid sample comprises at
least 12 % of said nucleic acid sample
at least 12%

5. The method of claim 1 wherein said second nucleic acid sample comprises at least 50 % of said nucleic acid sample

5 6. The method of claim 1 wherein each of said non-identical sequences differs from the other non-identical sequences by at least 5 nucleic acid bases.

7. The method of claim 1 wherein each of said non-identical sequences differs from the other non-identical sequences by at least 10 nucleic acid bases.

10 8. The method of claim 1 wherein each of said non-identical sequences differs from the other non-identical sequences by at least 50 nucleic acid bases.

9. The method of claim 1 wherein each of said non-identical sequences differs from the other non-identical sequences by at least 1000 nucleic acid bases.

10 10. The method of claim 1 wherein said NA sample is DNA.

11. The method of claim 1 wherein said NA sample is genomic DNA.

20 12. The method of claim 1 wherein said first nucleic acid sample is cDNA derived from RNA or mRNA.

13. The method of claim 1 further comprising the step of amplifying at least one of the non-identical sequences in said second nucleic acid sample.

25 14. The method of claim 13 wherein said step of amplifying is performed by a polymerase chain reaction (PCR).

15. The method of claim 1 wherein the entire method is performed in a single reaction vessel.

16. The method of claim 1 wherein said step of fragmenting the first nucleic acid sample comprises digestion with at least one restriction enzyme.

17. The method of claim 1 wherein said step of fragmenting the first nucleic acid sample comprises digestion with a type IIIs endonuclease.

18. The method of claim 1 wherein said adaptor sequences comprise PCR primer template sequences.

19. The method of claim 1 wherein said adaptor sequences comprise tag sequences.

20. The method of claim 1 wherein said solid support is a magnetic bead.

21. The method of claim 1 wherein said mismatch binding protein is bound to a magnetic bead.

22. The method of claim 1 wherein said method for analyzing a nucleic acid sample comprises determining whether the nucleic acid sample contains sequence variations.

25 23. The method of claim 22 wherein said sequence variations are single nucleotide polymorphisms.

24. The method of claim 1 wherein the step of obtaining a DNA array comprises:

designing a DNA array to query DNA fragments which have been produced by the identical procedures used to obtain said second nucleic acid sample.

25. The method of claim 24 wherein the step of designing further requires
5 predetermining the sequences contained in said second nucleic acid sample.

26. The method of claim wherein said step of predetermining the sequences contained in said second nucleic acid sample is conducted in a computer system.

10 27. The method of claim 23 wherein said second nucleic acid sample is obtainable
by:

binding oligonucleotide probes containing a desired SNP sequence to magnetic beads to form probe-bead complexes; and

hybridizing said probe-bead complexes to said DNA sample;

15 exposing said hybridized DNA sample to a single strand DNA nuclease to remove single stranded DNA thereby forming a DNA duplex;

ligating a double stranded adaptor sequence comprising a restriction enzyme site to said DNA duplex;

digesting said DNA duplex with a restriction enzyme to release the magnetic bead;

20 and

isolating only those fragments containing said SNP sequence.

28. The method of claim 25 wherein said restriction enzyme is a Class II endonuclease.

25 29. The method of claim 23 wherein said second nucleic acid sample is obtainable
by:

exposing the DNA sample to a mismatch bonding protein;

employing a 3' to 5' exonuclease to remove single stranded DNA; and

employing a nuclease to remove single stranded DNA.

30. A method of screening for DNA sequence variations in an individual comprising:

5 providing said first nucleic acid sample from said individual;

providing a second nucleic acid sample by reproducibly reducing the complexity of said first nucleic acid sample to produce a second nucleic acid sample which may comprise a plurality of non-identical sequences whereby said second nucleic acid sample is obtainable by:

10 fragmenting said first nucleic acid sample to produce fragments and ligating adaptor sequences to said fragments;

fragmenting said first nucleic acid sample to produce fragments, denaturing said fragments, allowing some of said fragments to reanneal to form double stranded DNA sequences and removing said double stranded DNA sequences.

15 amplification by arbitrarily primed PCR;

hybridizing said first nucleic acid sample to an oligonucleotide probe bound to a solid support;

hybridizing said first nucleic acid sequence to a mismatch binding protein;
providing a nucleic acid array;

20 hybridizing said second nucleic acid sample to said array; and

analyzing a hybridization pattern resulting from said hybridization.

31. The method of claim 30 wherein said sequence variation is a SNP.

25

32. The method of claim 31 wherein said SNP is associated with a disease.

33. The method of claim 31 wherein said SNP is associated with the efficacy of a drug.

34. A method of screening for DNA sequence variations in a population of individuals comprising:

providing said a first nucleic acid sample from each of said individuals;

5 providing a second nucleic acid sample by reproducibly reducing the complexity of said first nucleic acid sample to produce a second nucleic acid sample which may comprise a plurality of non-identical sequences whereby said second nucleic acid sample is obtainable by:

fragmenting said first nucleic acid sample to produce fragments and ligating adaptor sequences to said fragments;

10 fragmenting said first nucleic acid sample to produce fragments, denaturing said fragments, allowing some of said fragments to reanneal to form double stranded DNA sequences and removing said double stranded DNA sequences.

amplification by arbitrarily primed PCR;

15 hybridizing said first nucleic acid sample to an oligonucleotide probe bound to a solid support;

hybridizing said first nucleic acid sequence to a mismatch binding protein;

providing a nucleic acid array;

hybridizing said second nucleic acid sample to said array; and

20 analyzing a hybridization pattern resulting from said hybridization.

35. The method of claim 34 further comprising the step of compiling the analyses of each individual's hybridization pattern.

25 36. The method of claim 34 wherein said sequence variation is a SNP.

37. In a computer system, a method of designing an array comprising:

modeling specific enzymatic reactions between a known nucleic acid sequence and an enzyme;

obtaining the results of said modeled enzymatic reactions;

obtaining probe sequences based upon said results; and

5 designing an array to contain said probe sequences.

38. A method of analyzing a plurality of nucleic acid samples, comprising:

treating a first nucleic acid sample according to a defined procedure that produces a first population of fragments, the collective sequences of the fragments comprising a subset of the collective sequences present in the first nucleic acid sample,

10 determining abundance or composition of a subset of the population of the first population of fragments;

treating a second nucleic acid sample according to the defined procedure to produce a second population of fragments containing corresponding fragments to the fragments in the first population;

15 determining abundance or composition of a subset of fragments in the second population having sequences corresponding to the subset of fragments in the first population.

13